REMARKS

Claims 1, 2, 43 and 46-48 are pending in the present application. In ¶5 on page 2 of the Office Action, claims 1, 43, 46, and 48 are rejected under 35 U.S.C. §103 (a) over the combined teachings of Lee et al., "Epitope Mapping of CCR5 Reveals Multiple Conformational States and Distinct but Overlapping Structures Involved in Chemokine and Coreceptor Function", J. Biol. Chem. 274:14 (April 2, 1999) pp. 9617-9626 ("Lee et al. 1999") and Furuta et al., "Capture of an Early Fusion-active Conformation of HIV-1 gp41", Nature Struct. Biol., 5(4) (April 1998), pp. 276-279 ("Furuta et al. 1998") The Examiner stated that Lee and colleagues (1999) provide monoclonal antibodies that bind to the HIV-1 chemokine coreceptor CCR5 and inhibit viral binding to said receptor. The Examiner stated that Furuta and associates (1998) provide a compound that prevents Env-mediated membrane fusion by binding to a fusion intermediate. The Examiner stated that therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine two known compounds that are capable of inhibiting viral replicative events into a single composition since this would provide a more efficient antiviral compound. The Examiner further stated that one of ordinary skill in the art would have also been motivated to employ such a composition in inhibitory methodologies to prevent HIV-infection.

In ¶6 on page 2 of the Office Action claims 2, 43, 47 and 48 are rejected under 35 U.S.C. §103(a) over the combined teachings of Lee et al. (1999) and Furuta et al. (1998), as

applied *supra* to claims 1, 43, 46 and 48, and further in view of Valenzuela et al., "Neutralizing Antibodies Against the V3 Loop of Human Immunodeficiency Virus Type 1 gp120 Block the CD4-Dependent and -Independent Binding of Virus to Cells", J. Virol. 71(11) (November 1997) pp. 8289-8298 ("Valenzuela et al. 1997"). The Examiner stated that Valenzuela and colleagues provide neutralizing monoclonal gp120-specific antibodies that block HIV-1 gp120 CD4-dependent and independent binding. The Examiner stated that therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine three known compounds that are capable of inhibiting viral replicative events into a single composition since this would provide a more efficient antiviral compound. The Examiner stated that one of ordinary skill in the art would also have been motivated to employ such a composition in inhibitory methodologies to prevent HIV-infection.

Applicants respectfully traverse the rejection of claims 1, 2, 43 and 46-48 under 35 U.S.C. §103(a) for the reasons which follow.

It is well settled in the law that evidence of unexpected results obtained with the use of a claimed composition or method may serve to overcome a rejection of the subject claims based on 35 U.S.C. §103(a). The Examiner's rejection of, e.g., claim 1 directed to a two-component admixture is premised upon the disclosures of two references, wherein it is alleged that each said reference independently describes one of the two components of the claimed composition. AS to the three-component admixture, the Examiner has combined the disclosures

of Lee et al. and Furuta et al. with a third reference which is alleged to separately describe the third component of the claimed admixture. Without conceding that the three references cited by the Examiner do, in fact, individually disclose the components of the admixtures recited in applicants' claims, but assuming for the sake of argument that this is so, applicants contend that a significant and unexpected synergistic effect is achieved by combining the subject compounds into an admixture, versus wherein these compounds are separately administered, as disclosed in the prior art. Applicants contend that the wholly unexpected and superior synergistic results achieved with the admixtures of their invention, in contrast to when they are taken separately, is sufficient to overcome the presumption by the Examiner that one of ordinary skill in this art would find a suggestion in the cited prior art to combine their disclosures to achieve the presently claimed invention.

As disclosed in applicants' specification, the Combination Index ("CI") method of Chou and Talay was one of the methods used to quantitatively analyze the synergistic, additive and/or antagonistic effects achievable with various admixtures. As stated, e.g., at page 12, lines 22-23, "CI<1 indicates synergy, CI=1 indicates additive effects, and CI>1 indicates antagonism."

Figure 4D clearly illustrates the synergistic effect on the inhibition of HIV-1 infection which occurs due to the administration of a two-component admixture prepared according to applicants' invention. The admixture comprises the CCR5 coreceptor inhibitor PRO 140 in combination with the fusion

inhibitor T-20. Figure 4D lists four separate formulations of the admixture having inhibition percentages ranging between 50-95%. The indicated CI value for formulations achieving 50% inhibition and those which achieve 95% inhibition is 0.56. For formulations resulting in 70% and 90% inhibition, the CI value is 0.55. Since CI<1 indicates synergy, CI values of 0.56 and 0.55 achieved with two-component admixtures prepared according to the invention (see, e.g., claim 1) strongly evidence the fact that these compositions provide a substantial synergistic effect in the inhibition of HIV-1 infection, in contrast to the degree of inhibition achieved with the components taken separately.

A further indicator of the synergistic effect produced by the admixture described in Figure 4D is the dose reductions shown in the subject Figure. That is, the observed synergies between the components of the admixture translate into significant reductions in the amounts of PRO 140 and T-20 needed for inhibition. By way of example, as shown in Figure 4D inhibition of viral entry by 95% requires 12nM of PRO 140 used alone, 156nM of T-20 used alone, **or** 56.8 nM of a **combination** containing 1.8nM PRO 140 and 55 nM of T-120. The combination reduces the doses of PRO 140 and T-20 required to achieve the same inhibitory effect as the components taken separately by 6.7- and 2.8-fold, respectively.

Similar synergistic results have been achieved with three-component admixtures prepared in accordance with, e.g., claim 2 of the present application. For example, Figure 22 demonstrates the synergistic effect achieved by applicants with the use of an admixture composed of PRO 140, T-20 and the

fusion protein PRO 542. As shown in the figure, the CI values achieved with the use of this three-component admixture range between 0.18 and 0.24. As each of these CI values is <1, there is clear evidence of the synergistic effect on inhibition achieved due to the subject admixture. The CI values achieved with the three-component admixture described in Figure 22 are, moreover, significantly lower than the 0.55-0.56 range of CI values achieved with the two-component admixture according to the invention as illustrated by Figure 4. Thus the three-component admixture achieves an even greater synergistic effect than the two-component admixture, although the two-component and the three-component admixtures claimed by applicants are both clearly synergistic when contrasted to the results achieved with the various components when separately administered.

As to the dose reductions achieved with the use of the three-component admixture described in Figure 22, a composition producing, for example, 90% inhibition results in a 21-fold dose reduction in PRO-140, an 8.4-fold dose reduction in PRO 542 and 7.4-fold dose reduction in T-20, versus when these components are separately administered.

Claims 1, 2, 43 and 46-48 pending in the present application are entirely commensurate in scope with the showing of unexpected results. Claims 1 and 2 are directed, respectively, to two-component admixtures and three-component admixtures of compounds performing the functions recited in the subject claims, i.e., (1) binding to a CCR5 receptor; (2) retarding gp41 from adopting a conformation capable of mediating fusion of HIV-1 to a CD4+ cell by binding non-covalently to an

epitope on a gp41 fusion intermediate; and (3) retarding attachment of HIV-1 to a CD4+ cell by retarding binding of HIV-1 gp120 envelope glycoprotein to CD4 on the surface of the CD4+ cell. Figures 4D and 22 are directed to specific examples of such two-component and three-component admixtures, respectively, wherein the compounds in these admixtures perform the respective functions set forth above. In addition, claims 43 and 46-48 are directed to methods of inhibiting infection of a CD4+ cell utilizing the compositions of, respectively, claims 1 and 2. Figures 4D and 22 both set forth applicants' experimental results achieved through the use of compositions produced according to the invention for inhibit HIV-1 infection. In view, therefore, of the correspondence between the scope of the pending claims and the showing of unexpected synergistic results provided by applicants, the Examiner is respectfully requested to reconsider and withdraw the rejection of claims 1, 2, 43 and 46-48 under 35 U.S.C. §103(a) as the invention recited by those claims is unobvious and therefore patentable over the prior art.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorney invites the Examiner to telephone either of them at the number provided below.

A fee of Four Hundred Seventy-Five Dollars ($475.00) is deemed necessary for filing this Amendment. A check for that amount is enclosed herewith. If any additional fees are due, authorization is hereby given to charge the amount of such required fee(s) to Deposit Account No. 03-3125.

Respectfully submitted,

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I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450

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